D-neuron in Schizophrenia Research

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Abstract

Although dopamine (DA) dysfunction is a well-known hypothesis for etiology of schizophrenia, molecular basis of mesolimbic DA hyperactivity has not yet been clarified. To explain this, modulating function of trace amines on DA neurotransmission and the decreased number of striatal D-neurons, trace amine-producing neurons, were considered. Notably, Trace Amine-Associated Receptor, Type 1 (TAAR1), a subtype of trace amine receptors, with a large number of ligands, including tyramine, β-phenylethylamine and methamphetamine that have influence on human mental state, is now regarded as a targeted receptor for novel neuroleptics. Reduced stimulation of TAAR1 on DA neurons in the midbrain ventral tegmental area (VTA) has been revealed to increase firing frequency of VTA DA neurons. The decrease of D-neurons in the striatum and nucleus accumbens of postmortem brains of patients with schizophrenia has been reported. This implies the decrease of trace amine synthesis and consequent reduction of the stimulation of TAAR1 on terminals of midbrain VTA DA neurons, and may lead to mesolimbic DA hyperactivity in schizophrenia. The decrease of striatal D-neurons of postmortem brains of schizophrenia might be due to neural stem cell dysfunction in the subventricular zone of lateral ventricle. The new "D-cell hypothesis", in which D-neurons and TAAR1 are involved, is in agreement with recent reports of TAAR1 research using animal models.

Keywords

Dopamine; D-neuron; Trace Amine; Schizophrenia; TAAR1

Introduction

Dopamine (DA) dysfunction (Hokfelt et al. 1974, Toru et al. 1982) glutamate dysfunction (Watis et al. 2008, Olbrich et al. 2008) neurodevelopmental deficits (Christison et al. 1989, McGlashan et al. 2000) or neural stem cell dysfunction (Reif et al. 2006, Duan et al. 2007) are well-known hypotheses for etiology of schizophrenia. DA dysfunction hypothesis suggested that mesolimbic DA hyperactivity caused positive symptoms such as paranoid-hallucinatory state of schizophrenia (Hokfelt et al. 1974, Toru et al. 1982). It is also explained by the efficacy of DA D2 blockers for paranoid-hallucinatory state and also by hallucino-genic acts of DA stimulants including methamphet-amine or amphetamine (Hokfelt et al. 1974, Toru et al. 1982). Glutamate dysfunction theory was induced by the fact that intake of phencyclidine (PCP), an antagonist of NMDA receptor, produces equivalent to negative symptoms of schizophrenia, such as withdrawal or flattened affect, as well as positive symptoms (Watis et al. 2008, Olbrich et al. 2008). The neurodevelopmental deficits hypothesis implicates that schizophrenia is the consequence of prenatal abnormalities resulting from the interaction of genetic and environmental factors (Christison et al. 1989, McGlashan et al. 2000). Neural stem cell dysfunction has also been shown to be a cause of schizophrenia (Reif et al. 2006, Duan et al. 2007). Although mesolimbic DA hyperactivity (Hokfelt et al. 1974, Toru et al. 1982) has been well documented in pathogenesis of schizophrenia, the molecular basis of this mechanism has not yet been detailed. In the present article, the author hypothesized the involvement of striatal D-neurons and trace amine-associated receptor, type 1 (TAAR1) in the pathogenesis of mesolimbic DA hyperactivity of schizophrenia (Ikemoto et al. 2003).

D-neuron

The "D-cell" described by Jaeger et al. in 1983 in the rat central nervous system and defined as "the non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cell" contains AADC but neither dopamine nor serotonin (Jaeger et al. 1983). It can also produce trace amines (Boulton 1974, Boulton & Juorio 1979), and may act as an APUD (amine precursor uptake and decarboxylation) system that takes up amine precursors and transforms them to amines by decarboxylation (Komori et al. 1991). The localizations of D-cells are specified into 14 groups, from D1 (the spinal cord) to D14 (the bed nucleus of stria terminalis) in caudo-rostral orders of the rat central nervous system using AADC immunohistochemistry (Jaeger et al. 1984a, b). In this usage, the classification term "D" means decarboxylation. In rodents (Tashiro et al. 1989, Komori et al. 1991, Mura et al. 2000), a small number of D-cells in the striatum have been rostrally described and confirmed to be neurons by electron-microscopic

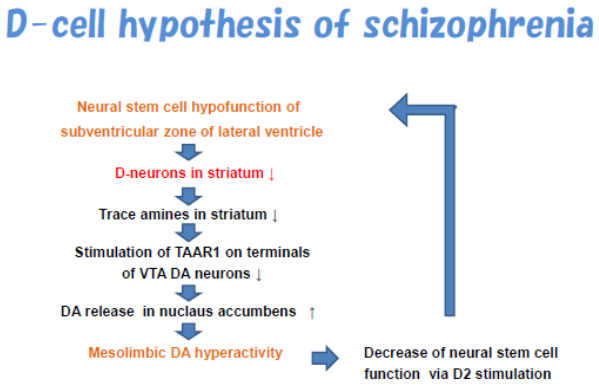
observation (Komori et al. 1991). The author with co-workers reported in 1997, "dopa-decarboxylating neurons specific to the human striatum" (Ikemoto et al.1997, 1998, Kitahama et al. 1998, 2009), that is, "D-neurons" in the human striatum (Kitahama et al. 1998, Ikemoto 2004) (classified to be D15) (Kitahama et al. 1998), and later, the reduction of the number of D-neurons in the striatum, including nucleus accumbens of patients with schizophrenia (Ikemoto et al. 2003, Ikemoto 2004).

Trace Amine-Associated Receptor, Type 1 (TAAR1)

Cloning of trace amine receptors in 2001 (Borowsky et al 2001, Bunzow et al. 2001), elicited enormous efforts to explore signal transduction of these G-protein coupled receptors whose genes are located on chromosome focus 6q23.1 (Miller 2011). The receptors have been shown to co-localize with dopamine or adrenaline transporters in monoamine neurons and to modulate the functions of monoamines (Xie & Miller 2007, 2009, Lindemann et al. 2008). The trace amine-associated receptor, type 1 (TAAR1) having a large number of ligands, including tyramine, β-phenylethylamine (PEA) and psychostimulants, for example metham-phetamine, 3, 4-methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD) (Bunzow et al. 2001, Zucchi et al. 2006, Miller 2011), has become a targeted receptor to explore novel neuroleptics (Bradaia et al. 2009, Revel et al. 2013). TAAR1 knockout mice showed schizophrenia-like behaviors with a deficit in prepulse inhibition, as well as greater locomotor response to amphetamine and released more DA (and noradrenaline) in response to amphetamine than wild type mice (Panas et al. 2010). It has been shown that TAAR1 has a thermoregulatory function (Wolinsky et al. 2007). It was clarified that increased stimulation of TAAR1 receptors on cell membranes of DA neurons in the midbrain ventral tegmental area (VTA) reduced firing frequency of VTA DA neurons (Bradaia et al. 2009, Panas et al. 2010, Revel et al. 2013).

A New "D-Cell Hypothesis" of Schizophrenia

A new theory, "D-cell hypothesis", to explain mesolimbic DA hyperactivity in pathogenesis of schizophrenia is shown in Figure. In brains of patients with schizophrenia, dysfunction of neural stem cells in the subventricular zone of lateral ventricle causes the decrease of D-neurons in the striatum and nucleus accumbens (Reif et al. 2006, Ikemoto 2008). This leads to the decrease of the amounts of trace amines in the nuclei, though direct evidences have not yet been demonstrated. Enlargement of the lateral ventricle (Degreef et al. 1992, Horga et al 2011), a usual finding documented in brain imaging studies of schizophrenia, is possibly due to dysfunction of neural stem cells of the subventricular zone (Reif et al. 2006, Duan et al. 2007).



The reduction of TAAR1 stimulation on DA terminals of VTA DA neurons, caused by trace amine decrease, would increase the firing frequency of VTA DA neurons (Bradaia et al. 2009, Panas et al. 2010), leading to the increase of DA release in the nucleus accumbens, and then resulting in mesolimbic DA hyperactivity. It has been shown that D2 stimulation of neural stem cells in the striatum inhibited forebrain neural stem cell proliferation (Kippin et al. 2005). Then, striatal DA hyperactivity may accelerate D-neuron decrease, which accelerates hyperactivity of meso-limbic DA system. Actions of D2 blocking agents in pharmacotherapy of schizophrenia might partially be explained by the decrease of inhibition to forebrain neural stem cell proliferations. It is consistent with clinical evidences that initial pharmacotherapy using D2 blockers is proved to be critical to prevent progressive pathognomonic procedures of schizo-phrenia.

Conclusions

The D-neuron, i.e., the trace amine-producing neuron, is a clue for pathogenesis schizophrenia. Further exploration of signal transduction of the D-neuron is essential.

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